THE PROMISING PATHWAY ACT
A BILL TO EXPEDITE POSITIVE PATIENT OUTCOMES

SUMMARY:

Expediting beneficial outcomes for patients is the sole purpose of this Act. For individuals with life-threatening, serious diseases, timely access to treatment is an essential element in the battle between life and death. The U.S. Food and Drug Administration (FDA) drug approval pathways must be continually rethought and redesigned to promote efficient access to effective treatments for patients with progressive diseases that, if left untreated, may significantly affect their daily lives or lead to premature death.

SUPPLEMENTARY INFORMATION:

The *Promising Pathway Act* (PPA) requires the FDA to establish a rolling, real-time, priority review pathway to evaluate provisional approval applications for drugs intended to treat, prevent, or diagnose serious or life-threatening diseases or conditions—including those that pose a threat of epidemic or pandemic (e.g., COVID-19). Under this pathway, provisional approval would be granted by the FDA to drugs demonstrating substantial evidence of safety and relevant early evidence of positive therapeutic outcome(s). The FDA currently has the legal authorities to establish such a pathway—in fact, they did so in the 1990s with the parallel track system—but creating a clearly defined, modernized pathway under PPA ensures such a pathway exists for the benefit of patients and can be reliably utilized by drug sponsors.

I. Background

On December 21, 2019, to make good on the government's promise to allow those with life-threatening illnesses better access potentially meaningful treatments, a first draft of PPA was introduced and interested parties were encouraged to submit questions, comments, and suggestions to be considered for a subsequent revision of PPA.

II. Comments on First Draft and Responses

Hundreds of Americans submitted feedback and proposed revisions—including personal stories, expert opinion, and stakeholder input. The great majority of comments either suggested changes to specific elements of PPA or requested clarification on certain elements of PPA.

A. Standard of review and how PPA differs from other FDA pathways and programs

(Comment 1) We received several comments seeking clarification on the standard of review for provisional approval and how it differs from the substantial evidence of safety and effectiveness standard utilized by the FDA in existing drug review pathways.

(Response 1) For a drug to be eligible for provisional approval status under PPA, it must be intended for the treatment, prevention, or medical diagnosis or serious or life-threatening diseases or conditions in which there is a reasonable likelihood that premature death or disability will occur without early medical intervention, a disease or condition that poses a threat of epidemic or pandemic, or a disease or condition that is associated with morbidity that substantially impacts day to day functioning. Additionally, to receive provisional approval status, a drug must demonstrate substantial evidence of safety and relevant early evidence of positive therapeutic outcome(s).

(Comment 2) Many comments requested clarification on how a new provisional FDA drug review pathway would differ from already established and utilized FDA drug review pathways—specifically, the Accelerated Approval pathway.

(Response 2) Several critical features distinguish provisional approval from accelerated approval. For instance, drugs being reviewed under the accelerated approval pathway are only accessible by patients enrolled in the drug's clinical trial, restricting widespread patient access to beneficial drugs until granted full approval. Encouraging the FDA to accept rolling applications

for time-limited provisional approval status for drugs that are safe and demonstrate relevant early evidence of positive therapeutic outcome(s) will facilitate access to promising drugs for a broader patient population faster than accelerated approval. Additionally, the accelerated approval pathway requires the use of validated surrogates, or endpoints, to measure the efficacy of a drug—which limits clinical trial design for rare or lesser-studied diseases. The provisional approval pathway, however, allows drug sponsors to incorporate the use of scientifically substantiated surrogates—surrogate endpoints other than those previously validated by the FDA—to predict a drug's clinical benefit based on epidemiologic, therapeutic, pathophysiologic, or other evidence for provisional approval. This difference in pathway requirements will increase innovation in clinical trial design and encourage sponsors to use real world data to ascertain the benefits of the drug without reducing the standard of effectiveness.

(Comment 3) Additionally, several commenters requested clarification on how a provisional approval pathway would impact clinical trial designs and enrollment.

(Response 3) PPA includes an important provision that requires the FDA to issue guidance that establishes clear protocols for enabling sponsors to submit rolling, real-time, mid-trial provisional approval applications. Importantly, this provision preserves the integrity of ongoing clinical trial design, development, and enrollment, as well as prohibits sponsors from being penalized for utilizing this pathway mid-trial—further promoting expedited and broad patient access to provisionally approved drugs. PPA is distinct from programs such as Right-to-Try and Expanded Access, also referred to as Compassionate Use, because under this pathway, patients will receive timely access to provisionally *approved* drugs. Whereas Right-to-Try and Expanded Access grant patients access to experimental, unapproved drugs.

B. Transparency and Patient Monitoring Requirements

(Comment 4) Many commenters, rightly, raised concerns with overall transparency relating to the new provisional approval pathway and questioned how patients and prescribers would receive timely information from the FDA and drug sponsors on provisionally approved drugs.

(Response 4) PPA establishes the requirement of patient registries for all provisionally approved drugs. Under PPA**,** the sponsor of a provisionally approved drug must ensure that all patients who use the drug participate in an observational registry and consent to the collection of, and submission of, data related to the patient's use of the drug until the drug receives full approval. Importantly, the registries must be readily accessible to patients—as well as allow approved researchers and medical professionals to access the aggregated and de-identified data for public health research. Additionally, patients will be immediately notified of any FDA decisions or adverse drug effects brought to light by review of any registry related to a provisionally approved drug—as the FDA is required under PPA to conduct an annual review of applicable patient registries. These registries can be run by third party governmental, for-profit, or nonprofit entities—but must track the effect of provisionally approved drugs on patients, including patient treatments, uses, length of use, side effects, scan results, and adverse drug effects. Finally, under PPA, any scientific, medical, academic, or health care journal publishing an article explaining, releasing, conveying or announcing research findings which were funded by the federal government shall be prohibited from publishing such research unless the article conveying the research findings is made publicly available on the journal's website without a paywall or charge three (3) months after it was first made available to subscribers or for purchase.

C. Post Market Controls

(Comment 5) A few commenters raised the issue of compliance with post-market approval requirements. Specifically, these commenters sought clarity about how the FDA would ensure drug sponsors met post-market approval requirements under the pathway.

(Response 5) Under PPA, the period of provisional approval is time-limited and effective for a two-year period. Drug sponsors may request provisional approval status renewal for subsequent two-year periods, up to a total of six years. The FDA will review the drug and renew provisional approval status based on real world data collected in the patient registries—which track patient usage of provisionally approved drugs—until the drug receives full approval or provisional approval expires. Additionally, under PPA, the FDA will review registry data as a part of approval for a sponsor's application for full approval or withdraw a drug's provisional approval status. Sponsors may apply for full approval for a drug at any time under the pathway. The FDA may also withdraw provisional approval of a drug with a significant number of reported adverse effects. Importantly, PPA establishes the position of Patient Advocate General within the Office of the Commissioner at the FDA to increase transparency and provide assistance to patients, as well as their families and caregivers.

Time-limited provisional approval incentivizes drug sponsors to collect diligently and submit drug data to the registries to renew their drug's provisional approval status. If a sponsor fails to meet post-approval requirements, the FDA will issue penalties and, in certain cases, withdraw provisional approval for the drug. For example, under PPA, if a drug sponsor has less than 90 percent of patients using a provisionally approved drug participating in the required registry—they will receive a $100,000 penalty, and if the violation is not corrected within 30 days the sponsor will be issued a $10,000 penalty every day the violation is not corrected. If patient participation is not at or above 90 percent within 6 months, provisional approval will be withdrawn.

D. Payment

(Comment 6) A great number of commenters—including patients and caregivers—raised the issue of payment in their comments. Specifically, commenters sought clarity on how patients would ultimately be able to afford drugs provisionally approved.

(Response 6) This issue is vitally important. Indeed, we cannot expect to expedite beneficial and positive patient outcomes if patients are ultimately unable to afford treatments provisionally approved under this pathway. Although there is no easy solution to this issue, PPA seeks to ensure *better* and *greater* access to provisionally approved treatments for patients. Specifically, PPA prohibits any group health plans, health insurance coverage providers, and federal health care programs (e.g., Medicare) from denying coverage of a provisionally approved drug on the basis of it being experimental and mandates that provisionally approved drugs be treated in the same manner as drugs fully approved by the FDA under other review pathways.

E. Priority Review and Evaluation Process

(Comment 7) Several commenters specifically asked how drug sponsors would request provisional approval under the provisional approval pathway and whether they would be required to pay user fees.

(Response 7) PPA allows for rolling, real-time FDA review of provisional approval applications, where the FDA may review various portions of new product applications as they become available, instead of waiting for a completed dossier. Under PPA, the FDA must evaluate provisional approval applications within 90 days of receiving a completed application. If the drug submitted for review under this pathway qualifies for FDA special designations, including but not limited to, designations for a rare disease or condition under the "Orphan Drug Act," all benefits of that designation shall be available for use under provisional approval, including any tax credits and waiving of FDA fees.